

That which is claimed is:

1. A multimeric receptor comprising at least one member of the steroid/thyroid superfamily of receptors and the ultraspiracle receptor.

5 2. A receptor according to claim 1 wherein said receptor is a heterodimer.

10 3. A receptor according to claim 1 wherein said receptor is a heterotrimer.

 4. A receptor according to claim 1 wherein said receptor is a heterotetramer.

15 5. A receptor according to claim 1 wherein said member of the steroid/thyroid superfamily of receptors is an insect-derived receptor.

20 6. A receptor according to claim 5 wherein said insect-derived receptor is the ecdysone receptor.

 7. A receptor according to claim 1 wherein said member of the steroid/thyroid superfamily of receptors is PPAR, VDR, TR α , TR β , RAR α , RAR β or RAR γ .

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12. A method according to claim 11 wherein said member of the steroid/thyroid superfamily of receptors is selected from ECR, PPAR, RAR, TR, or VDR.

5 13. A method according to claim 11 wherein said compound which prevents association of said member with the ultraspiracle receptor is an anti-ultraspiracle antibody.

10 ¹/₁₄. A method for modulating the expression of an exogenous gene in a subject containing:

15 (i) a DNA construct encoding said exogenous gene under the control of a steroid or steroid-like hormone response element; wherein said response element is not normally present in the cells of said subject,

20 (ii) a receptor which is not normally present in the cells of said subject, wherein said receptor, in the presence of its associated ligand and the ultraspiracle receptor, binds to said steroid or steroid-like hormone response element, and

25 (iii) ultraspiracle receptor;

30 said method comprising administering to said subject an effective amount of said associated ligand; wherein said ligand is not normally present in the cells of said subject; and wherein said ligand is not toxic to said subject.

35 ²/₁₅. A method according to Claim ¹/₁₄ wherein said receptor not normally present in the cells of the subject and said ultraspiracle receptor are provided to said subject by DNA construct(s) encoding said receptors.

³ 1~~6~~. A method according to Claim ² 1~~6~~ wherein said receptors are expressed under the control of a tissue specific promoter.

⁵ 17. A method according to Claim 14 wherein said exogenous genes are selected from wild type genes and therapeutic genes.

⁴ 1~~8~~. A method according to Claim ⁴ 1~~7~~ wherein said
10 wild type genes are selected from genes which encode gene products:

the substantial absence of which leads to the occurrence of a non-normal state in said subject; or

15 a substantial excess of which leads to the occurrence of a non-normal state in said subject.

⁶ 1~~9~~. A method according to Claim ⁴ 1~~8~~ wherein said
20 therapeutic genes are selected from those which encode gene products:

which are toxic to the cells in which they are expressed; or

which impart a beneficial property to said subject.

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8. A method to modulate, in an expression system, the transcription activation of a gene by a member of the steroid/thyroid superfamily of receptors in the presence of ligand therefor, wherein the expression of said gene is maintained under the control of a hormone response element, said method comprising:

exposing said system to at least the dimerization domain of the ultraspiracle receptor, in an amount effective to form a multimeric complex receptor with said member of the steroid/thyroid superfamily of receptors.

9. A method according to claim 8 wherein the dimerization domain of the ultraspiracle receptor is provided by exposing said system to compound(s) and/or condition(s) which induce expression of a gene encoding said dimerization domain.

10. A method according to claim 8 wherein said member of the steroid/thyroid superfamily of receptors is EcR, PPAR, VDR, TR, or RAR.

11. A method to modulate, in an expression system, the transcription activation of a gene by a member of the steroid/thyroid superfamily of receptors in the presence of ligand therefor, and in the further presence of the ultraspiracle receptor, wherein the expression of said gene is maintained under the control of a hormone response element, said method comprising:

exposing said system to compound(s) and/or condition(s) which prevent association of said member with ultraspiracle receptor, or fragments thereof, in an amount effective to prevent said association.

20. A method of inducing the expression of an exogenous gene in a subject containing:

5 (i) a DNA construct encoding an exogenous gene product under the control of a hormone response element; wherein said response element is not normally present in the cells of said subject,

10 (ii) DNA encoding a receptor which is not normally present in the cells of said subject, under the control of an inducible promoter; wherein said receptor, in the presence of its associated ligand and the ultraspiracle receptor, binds to said hormone response element,

15 (iii) ultraspiracle receptor, and

20 (iv) the associated ligand for said receptor which is not normally present in the cells of said subject;

25 said method comprising subjecting a subject to conditions suitable to induce expression of said receptor which is not normally present in the cells of said subject.

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21. A method of inducing expression of an exogenous gene product in a subject containing a DNA construct encoding said product under the control of a hormone response element; wherein said response element is not normally present in the cells of said subject, said method comprising introducing into said subject:

a receptor which is not normally present in the cells of said subject; wherein said receptor, in combination with its associated ligand and ultraspiracle receptor, binds to a hormone response element, activating transcription therefrom,

the ultraspiracle receptor, and
the associated ligand for said receptor.

22. A method for the expression of recombinant products detrimental to a host organism, said method comprising:

transforming suitable host cells with:

(i) a construct comprising a sequence encoding said recombinant product under the control of a hormone response element;

wherein said response element is not normally present in the cells of said host, and

(ii) DNA encoding a receptor not normally present in said host cells;

growing said host cells to the desired level in the substantial absence of hormone(s) which, in combination with said receptor, is capable of binding to said hormone response element, and

inducing expression of said recombinant product by introducing into said host cells the ultraspiracle receptor and hormone(s) which, in combination with said receptor not normally present in said host cells, bind to said response element.

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23. A method to distinguish the physiological effect of a first hormone receptor in a host from other hormone receptors in said host which respond to the same ligand, said method comprising:

5 replacing the ligand binding domain of said first receptor with a ligand binding domain from an exogenous receptor to produce a chimeric receptor maintained under the control of a tissue specific promoter;

10 wherein said exogenous receptor and the ligand to which the exogenous receptor responds are not normally present in said host; and

15 wherein said exogenous receptor, in the presence of its associated ligand, binds to a hormone response element, thereby activating said response element, and thereafter

20 monitoring the production of product(s) whose expression is controlled by said first hormone receptor when said host is exposed to ultraspiracle receptor and ligand to which said exogenous receptor responds.

24. A method to render mammalian hormone receptor(s) uniquely responsive to a ligand not endogenous to host(s) in which said receptor is normally found, said method comprising:

25 replacing the ligand binding domain of said receptor with a ligand binding domain from a second receptor;

30 wherein said second receptor is not normally present in said host; and wherein the ligand to which the second receptor responds is not normally present in said host.

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25. A method to determine the ligand(s) to which orphan receptor(s) responds, said method comprising:

monitoring a host cell containing a reporter construct and a hybrid receptor for expression of product(s) of said reporter construct upon contacting said cell with potential ligands for said orphan receptor and the ultraspiracle receptor;

wherein said reporter construct comprises a gene encoding a reporter molecule, operatively linked for transcription to a steroid or steroid-like hormone response element; wherein said response element is not normally present in the cells of said host;

wherein said hybrid receptor comprises:

the N-terminal domain and DNA binding domain of a member of the steroid/thyroid superfamily of receptors, wherein said member is not normally present in the host cells, and wherein said member, in the presence of its associated ligand, binds said response element, activating transcription therefrom, and

the ligand binding domain of said orphan receptor.

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26. An isolated DNA which encodes a polypeptide, wherein said polypeptide is characterized by having a DNA binding domain of about 66 amino acids with at least 9 Cys residues, wherein said DNA binding domain has:

- 5 (a) more than about 75 % amino acid identity in comparison with the DNA binding domain of hRXR-alpha,
- (b) less than about 60 % amino acid identity in comparison with the DNA binding domain of hGR
- 10 (c) less than about 60% amino acid identity in comparison with the DNA binding domain of hRAR α ,
- as well as functional fragments thereof.

15 27. A DNA according to Claim 26 wherein the polypeptide encoded by said DNA comprises a DNA binding domain with substantially the same sequence as that of amino acids 104-169 shown in SEQ ID NO:2.

20 28. DNA according to Claim 27 wherein the polypeptide encoded by said DNA has substantially the same sequence as that of amino acids 1-513 shown in SEQ ID NO:2.

25 29. DNA according to Claim 28 wherein said DNA comprises a segment with substantially the same nucleotide sequence as nucleotides 163 - 1704 shown in SEQ ID NO:1.

30 30. DNA according to Claim 29 which is pXR2C8.

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